Original papers

Cost-effectiveness analysis of acute kidney injury biomarkers in pediatric cardiac surgery

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Abstract

Introduction: Acute kidney injury (AKI) is significant problem in children with congenital heart disease (CHD) who undergo cardiac surgery. The economic impact of a biomarker-based diagnostic strategy for AKI in pediatric populations undergoing CHD surgery is unknown. The aim of this study was to perform the cost effectiveness analysis of using serum cystatin C (sCysC), urine neutrophil gelatinase-associated lipocalin (uNGAL) and urine liver fatty acid-binding protein (uL-FABP) for the diagnosis of AKI in children after cardiac surgery compared with current diagnostic method (monitoring of serum creatinine (sCr) level).

Materials and methods: We developed a decision analytical model to estimate incremental cost-effectiveness of different biomarker-based diagnostic strategies compared to current diagnostic strategy. The Markov model was created to compare the lifetime cost associated with using of sCysC, uNGAL, uL-FABP with monitoring of sCr level for the diagnosis of AKI. The utility measurement included in the analysis was quality-adjusted life years (QALY). The results of the analysis are presented as the incremental cost-effectiveness ratio (ICER).

Results: Analysed biomarker-based diagnostic strategies for AKI were cost-effective compared to current diagnostic method. However, uNGAL and sCys C strategies yielded higher costs and lower effectiveness compared to uL-FABP strategy. uL-FABP added 1.43 QALY compared to current diagnostic method at an additional cost of $8521.87 per patient. Therefore, ICER for uL-FABP compared to sCr was $5959.35/QALY.

Conclusions: Our results suggest that the use of uL-FABP would represent cost effective strategy for early diagnosis of AKI in children after cardiac surgery.

Key words: acute kidney injury; cardiac surgery; children; biomarkers; cost effectiveness analysis

Received: December 23, 2014 *Accepted: May 14, 2015*

Introduction

Children undergoing cardiac surgery for congenital heart disease (CHD) are at high risk to experience the development of acute kidney injury (AKI) in the immediate postoperative period (1-4) due to hypotension, inflammation, and nephrotoxic medication use (4). The incidence of AKI is in the range of 5-50% with an associated mortality of 20-79%, depending on the AKI definition used (2). Retrospective studies also suggest that the presence of AKI after cardiac surgery may be associated with the development of chronic kidney disease (CKD) (5-7). According to data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) on children with CKD stages 2–4 incidence rate of end-stage renal disease (ESRD) in the 1 year is 17% and after three years is 39% with median time to ESRD of 4.5 years (8). However, the outcome of children with ESRD is highly dependent upon availability of health care resources and applied renal replacement therapy (RRT). The aver-

age life expectancy of young adults who started RRT with a functioning graft during childhood is 63 years, while average life expectancy of young adults who remain on dialysis is 38 years (9). If to these dramatic data, we add extremely high costs of treatment for AKI and CKD patients, it is clear that there is a need to ensure a better outcome for AKI patients and better targeting of scarce resources for health care systems.

Increase in serum creatinine (sCr) concentration is used for the diagnosis of AKI. Unfortunately, increase in sCr concentration may be delayed compared to the already existing renal impairement and therefore administered therapy may be less effective. According to the literature, more than half of pediatric CHD patients (53%) develop AKI within the first 24h after the operation, and even 97.7% by 48h (2). Delayed diagnosis of AKI with sCr affects not only the worse outcome of AKI patients, but also higher resource use for health care systems.

On the other side, many new biomarkers offer promise for early detection of AKI (10-12). Since the ischemic stress during cardiopulmonary bypass (CPB) is the dominant etiological factor of AKI that affects proximal tubular integrity, in this study we examined the biomarkers that depend directly or indirectly on the function integrity of the proximal tubules: neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein (L-FABP), cystatin C (CysC). NGAL, which is synthesized in the systemic and renal pool, secreted by the thick ascending limb of loop of Henle and collecting ducts, is largely reabsorbed in the proximal tubules by efficient megalin-dependent endocytosis (10). Thus, increase in urine excretion of NGAL is likely to occur when there is an injury to proximal renal tubular epithelium and/or increased synthesis in the distal nephrons. Because L-FABP is expressed predominantly in proximal tubules, tubular stress that causes AKI may up regulated renal L-FABP expression and then accelerates urinary excretion of L-FABP from proximal tubules (11). CysC is almost completely reabsorbed and catabolized by the normal proximal tubules. When they are damaged as happen during CPB, the concentration of CysC increases in serum (12). According to the study Peco *et al.*, serum CysC (sCysC), urine NGAL (uNGAL) and urine L-FABP (uL-FABP) may rise as soon as 2h after cardiac surgery and 24 to 48h before sCr increases (13). Based on this, we assumed that their measurement may facilitate the faster recognition of AKI and promote earlier institution of preventive therapies. In addition to assessment of effectiveness, there is a need to calculate the costs of new diagnostic strategies.

Potential benefits from the use of new biomarkers must be balanced against the additional costs including test cost, the cost of stay in hospital and the costs of all clinical outcomes. The most commonly used method for economic evaluation is incremental cost-effectiveness analysis (ICEA). It compares at least two strategies against each other regarding expected costs and expected health outcomes (14). The health outcomes are usually expressed as quality-adjusted life years (QALY). QALY takes into account both the quantity and quality of life generated by healthcare interventions (15). Economic evaluations are often based on the use of decision analytic modelling, decision trees and Markov models. Markov models are useful for diseases in which events may occur repeatedly over time, when the timing of events is important, and when important events may happen more than once (14).

Therefore, we developed a decision analytical model to calculate incremental cost-effectiveness of different biomarker-based diagnostic strategies which can be used in the clinical practice compared to current diagnostic strategy. Since the economic impact of a biomarker-based diagnostic strategy is little known, the aim of this study was to compare cost and effectiveness of novel kidney biomarkers and to perform the cost-effectiveness analysis of using sCysC, uL-FABP and uNGAL for the diagnosis of AKI in children after cardiac surgery compared with current diagnostic method (monitoring of sCr level).

Materials and methods

Base case model

The model simulates the detection of AKI after cardiac surgery, treatment of AKI patients, progression of AKI to CKD, and finally treatment of CKD in

a cohort of patients younger than 18 years until each member of the cohort dies or reaches 100 years of age. At first, we created the decision tree to depict different strategies for the diagnosis of AKI in pediatric patients following CPB: using of standard strategy (monitoring of sCr level) or alternative diagnostic strategies (application of three kidney biomarkers: sCysC, uNGAL and uL-FABP). Decision analytical model is presented in Figure 1.

Standard monitoring strategy

Probabilities for AKI development detected with sCr and in-hospital mortality were calculated from the study Peco *et al*. (13). That study included relatively homogenous cohort of 112 pediatric subjects who underwent CPB due to CHD. The primary outcome was AKI development, defined as at least 25% decrease in the estimated creatinine clearance (eCCl) from pre-operative baseline at 48h after surgery, where eCCl was assessed according to formula of Schwartz et al. (16). Based on that, patients were divided into the AKI and non-AKI groups. The AKI was developed in 18 patients (16.1%). Secondary outcome included severity of AKI based on the pediatric modified RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease) (pRIFLE) criteria for diagnosis of AKI (17). pRIFLE scores were calculated using eCCl criteria with "Risk (R)" defined as eCCl decrease of 25% from baseline, "Injury (I)" defined as eCCl decrease of 50%, and "Failure (F)" defined as eCCl decrease of 75% or need for dialysis.

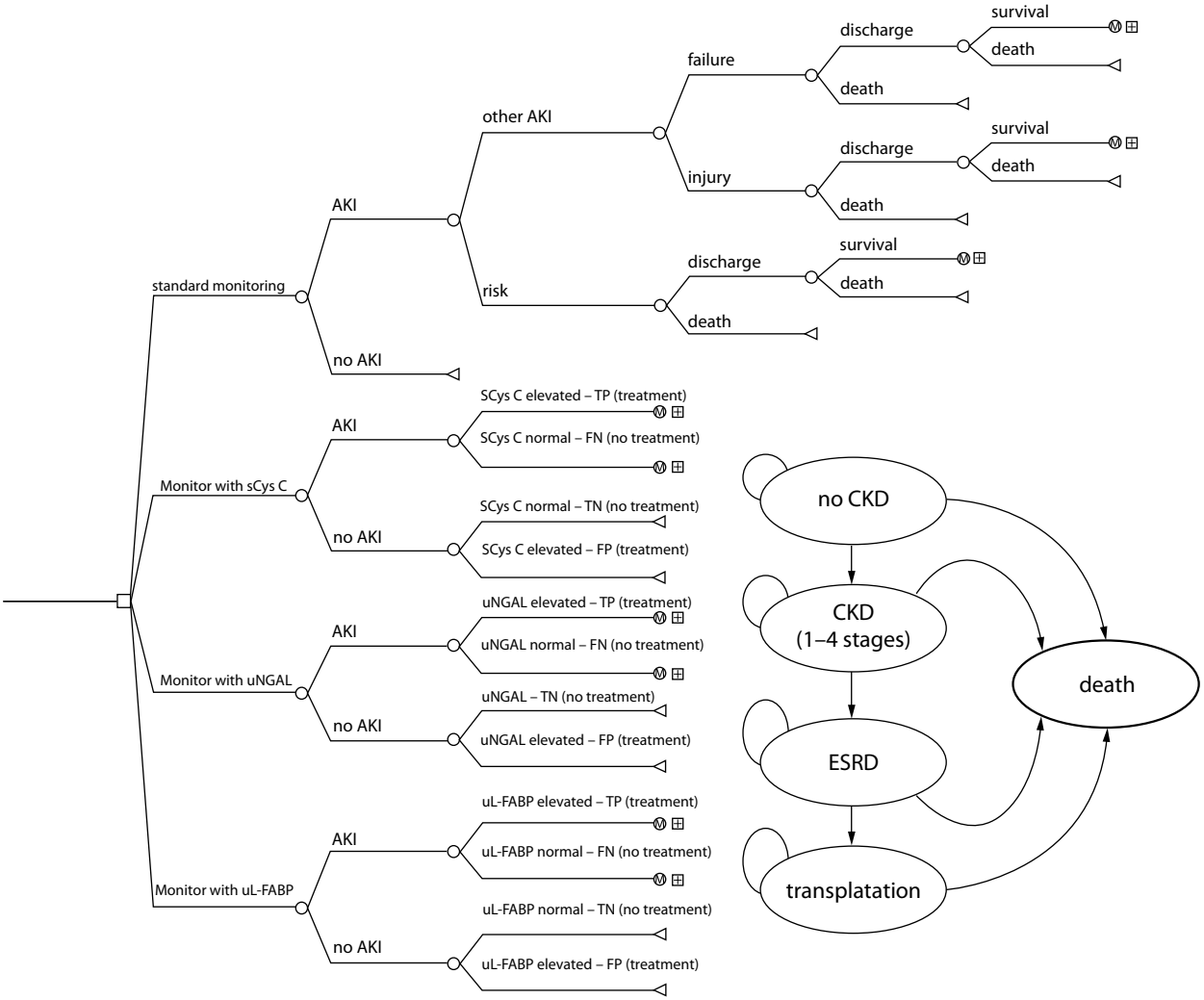

Figure 1. Decision analytical model used to assess new biomarkers serum cystatin C (sCysC), urine neutrophil gelatinase-associated lipocalin (uNGAL) and urine liver fatty acid-binding protein (uL-FABP) for the diagnosis of acute kidney injury (AKI) in children after cardiac surgery compared with standard monitoring (serum creatinine (sCr) level). Chronic kidney disease (CKD); end-stage renal disease (ESRD); true positive (TP); false positive (FP); true negative (TN); false negative (FN).

Furthermore, we also included probabilities for progression of renal disease and postdischarge death in patients who had an AKI episode. Here we used data from the few studies of monitoring transition from AKI to CKD that have been implemented until now (6,7).

Alternative diagnostic strategies

In alternative diagnostic strategies, AKI diagnose was based on clinical application of three kidney biomarkers: sCysC, uNGAL and uL-FABP, which showed good accuracy for early AKI diagnosis after cardiac surgery. Based on the data from the study Peco *et al*. (13) for sensitivity (Se) and specificity (Sp) we calculated the following parameters: true positive (TP), false positive (FP), true negative (TN) and false negative (FN) for alternative strategies with sCysC, uNGAL and uL-FABP at 2h after surgery (Table 1).

Markov model

If the AKI is present, patient will enter the Markov model, which was created to compare the lifetime cost associated with using of sCysC, uNGAL and uL-FABP with sCr for the diagnosis of AKI. In our study, the Markov model consists of following health states: no CKD, CKD (1-4 stages), ESRD, transplantation and death. Transition probabilities were taken from the cited sources (6-8,13,18-20), either as direct value or calculated on the one year probability assuming the constant rate (21). All Probabilities that were used in this model and their sources are listed in Table 2.

QALYs are calculated by multiplying the duration of time spent in a health state by utility score. Utility score was defined as value between 0 and 1, where 0 represents death and 1 represents a health state equal to perfect health (15). We obtained utility data from the Cost-Effectiveness Analysis (CEA) registry database (22), and the values are also presented in the Table 2.

TreeAge Healthcare module version 1.5.2 (TreeAge Software, Inc, Williamstown, USA) was used to create the model and conduct the sensitivity analysis. The TreeAge is the software used in decision analysis in order to perform a comparative analysis of alternative courses of action.

Previous therapy as a result of the earlier diagnosis with sCysC, uL-FABP and uNGAL was assumed to be associated with improved clinical outcome. It was represented by an assumed percentage (25%) of AKI patients for whom outcome was improved by earlier institution of preventive therapies (Table 2) (23,24).

Costs

The cost-effectiveness analysis was performed from a third-party payer perspective. Due to that, only direct medical costs were taken into consideration. Costs of diagnostic testing, hospitalizations, nephrologist consultation and RRT were expressed in dollars ($) (25-30). Costs are summarized in Table 3.

The consumed diagnostic procedures included measurements of sCr, sCysC, uNGAL and uL-FABP concentrations. In the study Peco *et al*. (13), sCr levels were measured by a modification of the kinetic Jaffe reaction, so we used price list for sCr assay from St. John Hopkins hospital (25), since this method is generally used in laboratories. sCysC, uNGAL and uL-FABP were assayed using human-specific commercially available enzyme-linked im-

Table 1. Diagnostic characteristics of new biomarkers.

	Se	Sp	TP	FN	TN	FP
uL-FABP	1	0.86	1	0	0.86	0.14
sCys C	0.54	0.82	0.56	0.44	0.82	0.18
uNGAL	0.63	0.60	0.61	0.39	0.61	0.39

Se - sensitivity; Sp - specificity; TP - true positive; FP - false positive; TN - true negative; FN - false negative; uNGAL - urine neutrophil gelatinase-associated lipocalin; uL-FABP - urine liver fatty acid-binding protein; sCysC - serum cystatin C.

Table 2. Input variables used in base-case analysis.

Variable	Value	Source
Probabilities		
Development of AKI in pediatric patients during CS	0.16	(13)
Patients classified as pRIFLE-R	0.56	(13)
Patients classified as pRIFLE-I and pRIFLE-F	0.22	(13)
In-hospital mortality among pRIFLE-R patients	0.10	(13)
In-hospital mortality among pRIFLE-I and pRIFLE-F patients	0.25	(13)
Survival for AKI patients (3-5 years)*	0.80	(6)
Development of CKD among AKI patients	0.10	(7)
Development of CKD among AKI patients after early therapy	0.075	(23,24)
Progression to ESRD among children with CKD stages 2–4 (3 years)*	0.39	(8)
Transplantation after the development of ESRD (3 years)*	0.75	(18)
Mortality in pediatric dialysis and transplant patient (5 years)*	0.08	(19)
Annual mortality	varies by age	(20)
Utilities		
No CKD (children population)	0.93	(22)
CKD	0.85	(22)
ESRD	0.61	(22)
Transplantation	0.74	(22)
Death	0	

AKI - acute kidney injury; CKD - chronic kidney disease; CS - cardiac surgery; ESRD - end-stage renal disease; pediatric modified RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease) criteria (pRIFLE): "Risk (R)", "Injury (I)", "Failure (F)".
* - all transition probabilities were calculated on the one year probabilty assuming the constant rate.

munoassays (ELISA) (R&D Systems, Inc., Minneapolis, Minesota), on ELISA reader (LKB, Vienna, Austria) according to the manufacturer's recommendations. Since used ELISA kits contained the entire material required for the work, we calculated prices for biomarker assays only from charges for ELISA kits (26). The cost of the assay included consumption for calibration (7 points) and a reagent blank test, as was done in duplicate. In addition, it was calculated that each analysis was performed in triplicate.

In order to assess the viability of new biomarkers of AKI and the availability of incidence data for transition from AKI to CKD, we used cost for AKI threatment for pediatric populations in the United States. The Kids's Inpatient Database (KID) was designed to identify and track trends in hospital utilization, access, cost, and outcome across the United States (27). Furthermore, cost for generalist and specialist visits, screening and diagnosis of CKD was used from the study Hoerger *et al*. (28).

All costs and outcomes were discounted by 3%. The discounting was performed due to the differential timing of costs and consequences of the compared strategies. The 3% discount rate was used in line with the recomendation from the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine (14).

Cost-effectiveness analysis

The results of the analysis are presented as the incremental cost-effectiveness ratio (ICER) which represents additional costs per additional effectiveness of each alternative diagnostic strategy compared to "monitoring of sCr level". Cost-effectiveness threshold was set at $50000 per QALY gained, as recommended for the United States

Table 3. Direct medical costs used in model.

Cost item	Cost (dollars ($))	Source
Cr assay	14 $	(25)
CysC ELISA assay	18.94 $	(26)
NGAL ELISA assay	17.81 $	(26)
L-FABP ELISA assay	24.38 $	(26)
AKI (after cardiac surgery)	18323 $	(27)
CKD screening first visit	80.32 $	(28)
CKD screening afterward if first positive	62.64 $	(28)
CKD diagnosis (GFR<60)	214.75 $	(28)
Annual specialist follow-up (GFR < 60)	77.28 $	(28)
Annual generalist visits (3 *per* year)	120.48 $	(28)
CKD in children	38893 $	(27)
ESRD first year	72348 $	(29)
ESRD subsequent year	59963 $	(29)
Kidney transplant in children	70193 $	(27)
Maintenance post-transplant	13749 $	(30)

AKI - acute kidney injury; CKD - chronic kidney disease; ESRD - end-stage renal disease; GFR - glomerular filtration rate; Cr - creatinine; NGAL - neutrophil gelatinase-associated lipocalin; L-FABP - liver fatty acid-binding protein; CysC - cystatin C; ELISA - enzyme-linked immunoassays.

health care system (31). If the ICER is lower than the set threshold, the strategy is considered to be cost-effective.

Sensitivity analysis

Sensitivity analysis was conducted for factors that could possibly restrict the generalisability of the study results. Probabilistic sensitivity analysis was used to test the uncertainty of the model. Ten thousand simulations were performed. In every simulation, each input parameter (probability, cost and utility) was sampled from the defined distribution of that parameter (21). The discount rate was varied from 0% (undiscouted) to 5% (14).

Results

Base-case results compared lifetime costs and associated QALY of current diagnostic method (monitoring of sCr level) with cost and QALY of new biomarker-based diagnostic strategies (Table 4). The cost-effectiveness ratios for all strategies were quite low, between $1485/QALY for sCr and $3579/QALY for uNGAL. ICER for all new biomarkers were well below the set threshold of $50000/QALY. However, uNGAL and sCys C were dominated strategies, meaning strategies with higher costs and lower effectiveness compared to uL-FABP strategy. uL-FABP added 1.43 QALY compared to current diagnostic method at an additional cost of $8521.87 per patient. Therefore, the ICER for uL-FABP compared to sCr was $5959.35/QALY.

Sensitivity analysis results

Scatterplot of cost and QALY differences for new biomarkers are presented at the Figure 2 and Figure 3. The diagonal line represents a cost-effectiveness threshold of $50000/QALY gained. The probabilistic sensitivity analyses indicated that the uL-FABP strategy was cost-effective for all 10000 simulations at the specified threshold (point below and to the right of the line) (Figure 2). For two

Table 4. ICER of base-case model (all strategies compared to current diagnostic method – monitoring of sCr level).

Strategy	Cost ($)	Incremental cost ($)	Effectiveness (QALY)	Incremental effectiveness (QALY)	C/E ($/QALY)	ICER ($/QALY)
sCr assay	5607.50	-	3.78	-	1483.46	-
uL-FABP assay	14126.37	8521.87	5.21	1.43	2711.39	5959.35
sCysC assay	15303.57	9696.07	5.15	1.37	2971.57	7077.42
uNGAL assay	18462.65	12855.15	5.16	1.38	3578.03	9315.33

QALY - quality-adjusted life years; sCr - serum creatinine; uNGAL - urine neutrophil gelatinase-associated lipocalin; uL-FABP - urine liver fatty acid-binding protein; sCysC - serum cystatin C.

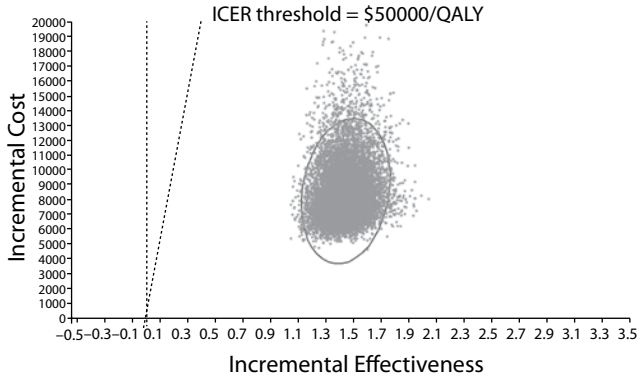

Figure 2. Cost-effectiveness scatterplot of incremental costs and incremental effects of urine liver fatty acid-binding protein (uL-FABP) *vs*. current diagnostic method (serum creatinine (sCr) level).

other biomarkers (uNGAL and sCys), sensitivity analysis shows ICER was above the set threshold (points above and to the left of the line (Figure 3).

Discussion

Because health care budgets and resources of all systems have become more restrictive, many have increasingly supported cost-effectiveness analysis and related analytical methods to assess the impact of new diagnostic and therapeutic interventions to facilitate efficient allocation of scarce resources (23).

The results of our study show that analysed biomarker-based diagnostic strategies for AKI are cost-effective compared to current diagnostic method. However, uNGAL and sCys C strategies yielded higher costs and lower effectiveness compared to uL-FABP strategy. Additional QALY and cost for uL-FABP compared to current diagnostic method were 1.43 and $8521.87 respectively. The ICER for uL-FABP compared to sCr was $5959.35/QALY and that was lower than specified threshold ($50000/QALY). Therefore, our results suggest that the use of uL-FABP would represent an economically advantageous strategy for early diagnosis of AKI in children after cardiac surgery. Higher price for uL-FABP assay compared to sCr, and even sCysC and uNGAL assays, is fully compensated by its better diagnostic characteristics (Se and Sp) for early detection of AKI, which would enable timely and more efficient treatment of patients. This would lead to significantly improved outcomes for AKI patients and finally lower long-term resource consumption. Shaw and colleagues (23) applied cost-effectiveness analysis and compared uNGAL to standard monitoring in 67-year-old male patient undergoing coronary artery bypass graft surgery. According to results from that study uNGAL was cost-effective strategy and the differences between costs and QALYs increased as the treatment effect rose (23). Difference in results beetwen our study and Shaw et al. study was in chosen population and number of examined parameters. Children after cardiac surgery are an ideal type of patient in whom studying of AKI biomarkers is possi-

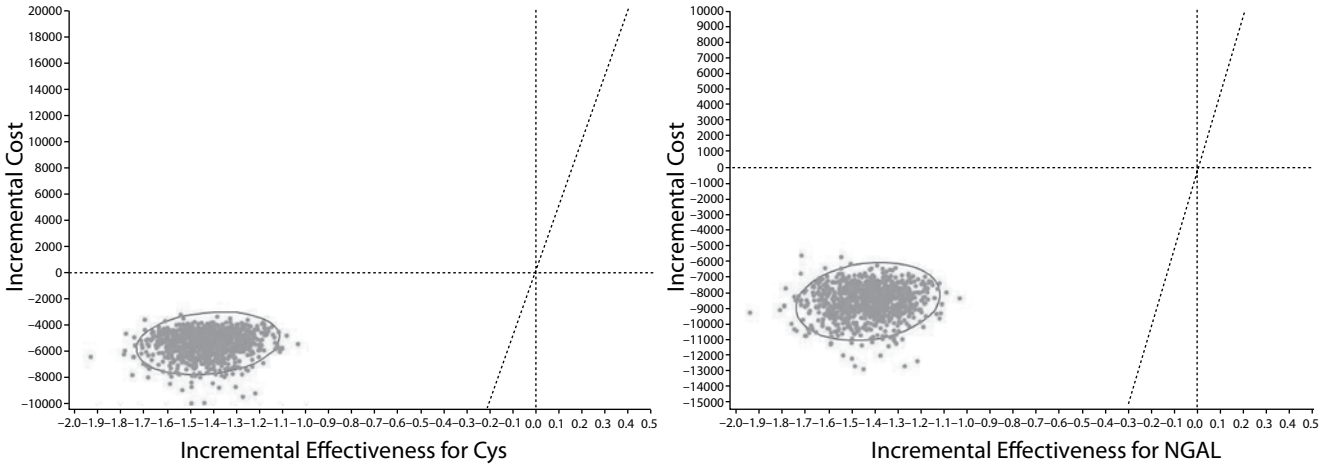

Figure 3. Cost-effectiveness scatterplot of incremental costs and incremental effects of urine neutrophil gelatinase-associated lipocalin (uNGAL) and serum cystatin C (sCysC) *vs*. current diagnostic method (serum creatinine (sCr) level).

ble without the influence of co morbidities that complicate similar studies in adults, such as diabetes, chronic hypertension and atherosclerosis. Since this is the first economic evaluation of CysC and L-FABP, there are no data available for comparison to our study.

In our study sensitivity analysis was performed to determine how changes in values for the variables would affect the findings. In this way, we varied data for the incidence of AKI development after cardiac surgery with an associated mortality, since these data differ considerably between studies, primarily because of the different criteria that was used to set AKI diagnosis. Also we varied diagnostic characteristics of assays (Se and Sp), since our analysis is based on the results of one study, Peco *et al*. (13). Using the data of several studies about diagnostic characteristics of assays for the economic study is not adequate, because the various studies used assays from different manufacturers and therefore different prices. Generalisability of the study results was confirmed because uL-FABP remained dominant throughout a wide range of values for the underlying variables. After applied sensitivity analysis, ICER values for uNGAL and sCys were above the set threshold and that confirmed that uL-FABP have the best cost-effectivness among analysed biomarkers (Figure 3).

In addition to the potential application of uL-FABP for the early diagnosis of AKI after cardiac surgery we should mention the following: urinary diagnostic has several advantages, including the noninvasive nature of sample collection, which is very important in pediatric populations. Furthermore, uL-FABP may be also used to predict severity of AKI, as it distinguish between R and severe AKI categories, also uL-FABP shows the best correlations with CPB and aorta clamp (AC) time, risk adjustment for congenital heart surgery (RACHS) score (13). Therefore, our recommendation is development of algorithm that will based on clinical parameters (patient age, CPB and AC time, RACHS score), that would enhance assessment of risk for AKI development. A high score in this algorithm and increased value of uL-FABP at 2h after surgery could perform selection of patients in whom treatment should be applied immediately. Applicability of the proposed algorithm should be tested in properly designed clinical trials.

Our finding highlights the importance of effective diagnostic tests, which accurately selects patients with AKI who need early intervention or modification of therapy to mitigate severe and permanent kidney injury, as opposed to unaffected patients who will not benefit. It is clear that early diagnosis of AKI requires a good and not expensive screening test with high Se and small percentage of FN results, because it is important not to miss any ill person (32). In addition, it is important that applied analysis provides a rapid and accurate results. In this context, unlike uNGAL and sCys C biomarkers that have already developed rapid point-of-care (POC) tests, L-FABP biomarker still not have possibility of this type of analysis. Development of POC test for uL-FABP is desirable, because these tests have several advantages (rapid test results and smaller volumes of specimen needed for testing) (33).

AKI is a major side effect of other medical procedures and can result from insults ranging from ischemia reperfusion injury following CPB surgery or renal transplant to damage from nephrotoxic agents such as contrast used or cysplatin. We believe that the application of biomarkers could improve the diagnosis of AKI and reduce costs additionally in these clinical conditions, but it has to be proven in especially designed studies.

Findings of our study can also provide important information for pharmacological research studies. Results in this field would certainly contribute to the better outcome of patients with AKI and enable significant savings as compared to expensive dialysis. There are already encouraging results in the form of application of high-dose fenoldopam, a selective dopamine-1 receptor, that positively affect on renal function and organ perfusion during CPB in infants with CHD (24).

The main limitation of our study is method used to determine the concentration of biomarkers (ELISA), because if we are talking about early diagnosis of AKI, it is certainly not desirable to wait for the result of biomarkers for 6-7 h. Also, our study included only direct medical costs since the study

perspective was a third-party payer. No indirect cost of CKD were included in the analysis.

Conclusions

Our results suggest that among all examined biomarkers only uL-FABP had acceptable ICER and the use of uL-FABP would represent cost-effective strategy for early diagnosis of AKI in children after cardiac surgery. The higher prices for commercial uL-FABP test will not change the conclusion of our study because the sensitivity analysis demonstrated that significant variations in the price will not influence on ICER value.

Acknowledgement

This study was financially supported by grant from the Ministry of Education, Science and Technological Development Republic of Serbia (Project Number 175035).

Potential conflict of interest

None declared.

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